Scalp Cooling

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Chemotherapy-induced alopecia (CIA), a side effect with high impact, can be prevented by cooling the scalp during the administration of some cytotoxic drugs. Scalp cooling is a well-known method to try to prevent CIA during the administration of cytotoxic drugs for solid tumors. Using scalp cooling, liquid refrigerant is pumped as coolant through a cooling cap that is placed on the head of the patient. In general, scalp cooling is started 20–45 min prior to, during, and up to 20–150 min after the chemotherapy infusion.

Keywords: chemotherapy-induced alopecia ; scalp cooling ; paclitaxel ; clearance

1. Introduction

Chemotherapy-induced alopecia (CIA) is a commonly feared side effect of systemic anti-cancer treatment.[1] It can affect a patient's quality of life dramatically and is one of the most distressing and adverse aspects of anti-cancer treatment, particularly for women.[2] Scalp cooling is a well-known method to try to prevent CIA during the administration of cytotoxic drugs for solid tumors.[3][4] Scalp cooling results in a locally decreased blood flow due to vasoconstriction, resulting in a lower chemotherapy concentration at the root of the hair follicles and thereby, hopefully, in hair preservation.[5] The pharmacokinetics and pharmacodynamics of several drugs are influenced by body temperature.[6] Deep scalp cooling (4 °C), lasting for 20–45 min before, continued during and lasting for up to 150 min after chemotherapy infusion, may potentially lead to a temperature reduction of the whole body. This drop in body temperature may lead to alterations in pharmacokinetics.[6] This is of clinical relevance as changes in pharmacokinetics may lead to under- or over-exposure to the drug of interest. In a previous study, a physiologically based pharmacokinetic model (PBPK) of doxorubicin was modified to include a scalp skin compartment. The results of the model showed that maximum and average concentrations of doxorubicin in the scalp skin compartment were reduced by a factor of 3.6 and 1.6, respectively, during scalp cooling. These effects were due to reduced tissue perfusion and can positively influence the survival of hair follicles. However, mass transfer characteristics were not considered.[7][8]

At present, there are no data available regarding the effects of scalp cooling on the pharmacokinetics of the cytotoxic drugs that are infused.

The severity of CIA, but also the success rate of scalp cooling, depends on the type of anti-cancer treatment used, its dose, method of administration and schedule of treatment.[9][10] Scalp cooling in patients treated with taxane-based chemotherapy such as paclitaxel, a widely used antineoplastic agent for the treatment of several cancers (e.g., breast, ovarian and esophageal cancer),[11][12][13] led to hair conservation in more than 50%, of patients, depending on the dose, compared with those who received no scalp cooling.[14] Scalp cooling is therefore offered as a part of standard treatment.

2. Effect of Scalp Cooling on the Pharmacokinetics of Paclitaxel

Blood samples for the pharmacological analyses were collected during one of the paclitaxel administrations, not necessarily the first administration, at four predefined time points: pre-dose, 55 (5 min prior to the end of the paclitaxel infusion), 90 and 360 min after the start of the paclitaxel infusion.[15] In patients where paclitaxel was administered in a standard stepwise increase in infusion rates because of hypersensitivity during previously administered paclitaxel treatment, this was pre-dose, 85 (5 min prior to the end of the paclitaxel infusion), 120 and 360 min after the start of paclitaxel infusion. The samples were collected by venipuncture or cannula in 4.5 mL lithium heparin blood collection tubes and processed within 10 min by centrifugation for 10 min at 2500–3000× *g* at 4°C. Plasma was transferred into polypropylene tubes (1.8 mL Nunc Cryotube vials), which were stored at a temperature of minus 70 °C. Paclitaxel pharmacokinetics were measured in all plasma samples using a validated ultra-performance liquid chromatographic coupled to tandem mass spectrometry (UPLC-MS/MS) for precise quantification of paclitaxel plasma concentrations at the Laboratory of Translational Pharmacology of the Erasmus MC Rotterdam.[16] Non-linear mixed effects modeling was conducted using the software NONMEM.[17] A previously developed population pharmacokinetic model for paclitaxel,

[14] with two compartments describing the disposition and linear elimination, was used as a starting point. However, the model was here expanded to a three-compartment model to fit the data. Scalp cooling was tested for its effect on the model PK parameters.

Although the decrease in body temperature during scalp cooling at each site measured was small, the decrease was statistically significant different during scalp cooling for the measurement in the ear and axilla. There was no significant difference in temperature until 3h after scalp cooling was discontinued. Finally, half of the patients developed some form of hair loss despite scalp cooling. However, this was not associated with paclitaxel clearance.

Mild hypothermia (body cooling to 32 to 34°C for 12h to 48h) can alter the pharmacokinetic parameters of several drugs. [6] Although the mechanism(s) behind changes in drug levels due to hypothermia has not been fully elucidated, impaired hepatic metabolism is likely, possibly via its effect on cytochrome P450 metabolism. In a study in healthy volunteers, for example, the clearance of midazolam as an index of CYP3A4/5 metabolism decreased by 11% for every degree Celsius decrease in a core temperature of 36.5°C.[18]

In our analysis, a population PK model consisting of a central compartment with two peripheral compartments connecting to it was used to obtain clearances and volumes of distribution of each subject. Unlike PBPK models, these compartments have no anatomic or physiological significance. However, they can still be used to investigate the influence of subject characteristics (i.e., scalp cooling) on the predicted subject PK parameters describing the whole-body drug disposition.[19]

We hypothesized that the decrease in body temperature as a result of scalp cooling may influence the pharmacokinetics of paclitaxel. Although a small decrease in body temperature was found after 50 min of scalp cooling, which did not fully return to baseline after 5h, the absolute decrease was limited: 60% of the women had a temperature drop of less than just 1°C. This drop in temperature may be too small to demonstrate a difference in clearance of paclitaxel.

Scalp cooling is usually a good option to prevent hair loss for anti-cancer drugs with a short half-life or a rapid systemic distribution, such as paclitaxel.[10] However, it is unclear why some patients still develop CIA despite scalp cooling during such chemotherapy administration. Half of the women were found to have some form of hair loss, of whom more than 40% developed grade 2 alopecia (although no one developed full baldness). This is somewhat higher than mentioned in previous studies, probably due to differences in definition of CIA between these studies.[10] We found no clear difference between the patients who developed CIA and those who did not. If any, the mean temperatures were slightly lower among those women without CIA compared to those with CIA. It is important to emphasize that CIA was also not due to differences in paclitaxel clearance. Further research is needed to identify possible explanations to better advise future patients about the chance of hair preservation with scalp cooling.

3. Conclusions

Scalp cooling concomitant with paclitaxel did not reduce nor increase the clearance of paclitaxel. Therefore, it is unlikely that scalp cooling influences paclitaxel efficacy.

Finally, despite scalp cooling, half of the patients in our study developed a form of hair loss. Importantly, neither an association with difference in paclitaxel clearance nor a change in hair loss was found. Further research is warranted to optimize hair preservation in patients treated with paclitaxel.

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